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CHEMICAL & ENGINEERING

NEWS

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CHEMICAL & ENGINEERING NEWS

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MARCH 19, 1990

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■ **Rhône-Poulenc, Rorer Group sign an agreement to merge their pharmaceutical interests to form new health care company.** Page 7

■ **Polish environmental minister, Bronislaw Kamiński, succeeds in his efforts to garner funds from U.S., World Bank, among others for cleanup plan.** Page 8

■ **Food & Drug Administration approves further testing of Salk AIDS vaccine, other proposed anti-HIV vaccines, remedies.** Page 8

Cover: Photo by C&EN's James Krieger

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Science/Technology

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LETTERS

Graduate studies

SIR: I would like to respond to Elliot Scherr's letter concerning the relative ease of obtaining degrees in law, medicine, dentistry, and management compared to chemistry (C&EN, Jan. 15, page 2). As a law student with a Ph.D. (albeit in physics, not chemistry), I feel qualified to comment on his assertions, at least as far as law school is concerned.

My Ph.D. required 90 semester hours, 60 of which were course hours, over a five-year period. My J.D. degree will require 90 semester hours of courses over a three-year period, with a writing requirement that will take as much time and effort as a thesis. My law courses are not easier and do not require less work than my physics courses. The material is challenging and fully as intellectually rigorous as any class in physics. I spent one to two hours preparing for each classroom hour in graduate school; the rule of thumb in law school is three or more hours for each classroom hour. I worked hard in graduate school; I am working harder in law school.

Furthermore, there are no fellowships or assistantships for students in law, medicine, dentistry, or management. Unlike most graduate students in the sciences, students in these fields pay tuition and provide for their own living expenses. Many of my classmates work up to 20 hours per week in addition to attending school full time. I doubt they have many free weekends! I know I don't.

Mr. Scherr, please don't denigrate fields other than your own simply because you believe the work is easier or the starting salaries higher. A lawyer works just as hard as a physicist—or a chemist—does. Neither determines her own worth in the job market. Her employer does that.

Maria Reichmanis
Aiken, S.C.

SIR: I find myself in complete agreement with the opinion expressed in the letter by Elliot Scherr—namely, that poor financial incentive at the graduate student and postdoctoral levels is a major reason why fewer people are choosing careers in basic research. It is also a major cause of attrition among those who initially do opt for scientific careers.

As a married fourth-year chemistry graduate student who enjoys science greatly but who would also like to start a family sometime soon, I feel that I can speak with some authority on this issue. Quite frankly, financial concerns occupy my mind much more often than they should. These days, whenever someone asks me for advice regarding a career in science, I suggest that if they are not independently wealthy they should obtain a B.S. in engineering and then find a job.

There are ways to remedy this situation; for example, money. More specifically, the current stipend level for graduate students should be considered adequate for perhaps the first two years of graduate study. After completion of the usual requirements—comprehensive exams, course work, and research proposal defense—the stipend level should be increased substantially, say 30%. In a related matter, graduate students and their advisers should be required to submit a tentative timetable for completion of the student's Ph.D. by the beginning of the fourth year of graduate study. This would help reduce the incidence of long, financially uncertain stays in graduate school.

The postdoctoral pay scale is also poor, particularly in academia. Many of these positions offer salaries in the $18,000 to $20,000 range, which is, in my opinion, an outrageous sum to offer someone who has already completed between eight and 10 years of posthigh school education. I will almost certainly not pursue an academic career. University officials must redouble their efforts to secure adequate funding for research and reasonable pay scales for scientists. Industry must be persuaded to assume a share of this cost through governmental incentives (tax breaks) and university/industry partnerships. We must make it easier, in the financial sense, for gifted people to choose scientific careers.

Keith L. Constantine
Carnegie Mellon University

Percy Julian's achievements

SIR: The book review, "Blacks, Science, and American Education" (C&EN, Feb. 12, page 28), contains some statements about one black chemist, Percy L. Julian, that require correction, and some generalizations that need more careful consideration.

It is stated that Julian discovered cortisone, that he synthesized physostigmine, and that he was the first to synthesize the sex hormones. The facts are that Julian did prepare intermediates for the industrial production of steroid hormones, but he performed only one of

Photo by Dow Chemical's Anne Leugers

Raman spectrophotometer with CCD detector is used in pilot plants

damentals. The resulting quantitative analysis is linear up to 100% concentrations of analytes, she says, and turbid or opaque samples present no problems.

Leugers demonstrated analysis of a benzene-toluene stream in one second, as well as of a complex mixture of carbon tetrachloride, toluene, dioxane, and cyclohexane. In a real-world problem, the Dow team followed a polymerization reaction, sampling the spectrum every five seconds. They were able to study the mechanism of the addition of repeating units to the polymer chain. Leugers says it might be possible to feed optical cables from five different reactors to the same spectrophotometer.

The commercially available FT-Raman/IR spectrophotometer with

CCD is mounted in Spex Industries' FT-Raman/IR spectrophotometer

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CCD detector of Spex Industries uses the 752-nm output of a krypton ion laser for excitator, according to product manager Purcell. This excitation wavelength avoids not only fluorescence but also black-body radiation from darkly colored samples.

The system with spectrophotometer, CCD detector attachment, and data-collection software is priced at $60,000 (Circle 220).

Working with Job Bello, Purcell analyzed dry rice flour. He points out that after wetting with water and baking dry, even pure starch develops fluorescence, which interferes with Raman spectrometry. The Edison, N.J., workers also showed the recording of clear Raman spectra with such classic bad actors as rhodamine 6G and fluorescein isothiocyanate, which fluoresce strongly. They presented the Raman spectrum of a solid phthalocyanine that was opaque green-to-black in color.

Chemistry professor Alexander Scheeline of the University of Illinois, Urbana, has applied the combination of an échelle spectrograph with a CCD detector to investigations of species in plasma-enhanced chemical vapor deposition, a process used in semiconductor device fabrication. The spreading out of a wide spectral range allowed simultaneous measurements at multiple wavelengths with 0.03-nm resolution to minimize effects of what is called flicker noise.

Working with graduate students Cheryl A. Bye, Steven Rynders, and Duane L. Miller and supported by the National Science Foundation and Department of Energy, Scheeline observed Si-H in a plasma of silane and argon. Their computer program "pasted" the whole spectrum in strips on the CCD.

First they recorded the spectra in false colors, in which each color represented spectral intensity. Then they converted these to more conventional line spectra.

Staff scientist Michael J. Pelletier of Procter & Gamble's Miami Valley Laboratories, Cincinnati, Ohio, used the same approach to acquire Raman spectra of cyclohexane with 1-cm^{-1} resolution in one second. His band spectra were shown superimposed on the original false-color format.

A 5-nanosecond pulse from a 514.5-nm Nd:YAG (neodymium/yttrium-aluminum-garnet) laser was used by Pelletier to deliver a single 200-millijoule pulse to the sample. He suggests that the fast response of CCD detectors might make it possible to study irreversible processes with single, high-energy blasts of laser energy while avoiding interference from sample destruction.

Pelletier uses each adjacent cell of the CCD to represent 1 cm^{-1}. He described a computer-guided experiment in which two bands were 2 cm^{-1} apart. In this case, the bands would be resolved, because the data in each cell would be separated by one blank cell. But such bands could not be resolved if they were only 1 cm^{-1} apart. This is because data would show up in two adjacent cells, and the computer program would record them as part of one peak. □

Chiral drug analysis

Easily the most emotional issue in the Pittsburgh Conference technical sessions was that of chiral drugs. Of 1327 totally synthetic drugs marketed worldwide today, 528 are chiral, capable of existing as two or more optical isomers depending on the number of dissymmetric centers.

Often among enantiomers, only one is pharmacologically active, and the other or others are without effect, of different effect, toxic, or of unknown effect. Yet only 61 of the 528 chiral synthetic drugs are marketed as single enantiomers, while the other 467 are sold as racemates.

The Food & Drug Administration is expected within a couple of months to begin regulating the marketing of single enantiomers versus racemates in new drug submissions. A number of speakers explored the pharmacological implications of chiral drugs and presented recent

progress in developing analytical methods that will be needed to generate data for new drug approvals.

The regulation of chiral drugs as it is evolving in the U.S. and elsewhere will produce a boomlet among products sold to meet them. Market researcher Philip Rotheim of Business Communications Co., Norwalk, Conn., predicts in the U.S. alone that sales of what he calls stereoselective chiral technology products will grow at 17.5% annually to $2.8 billion in 2000 from $465 million in 1989. Included among these are analytical instruments and reagents, resolving agents, and chiral intermediates and catalysts.

Pharmacology professor John Caldwell of St. Mary's Medical School (Imperial College), London, outlined the pharmacological situation. Chirality plays no role in such processes as absorption, distribution, and secretion of drugs and metabolites, he says. These processes depend on passive transport across lipid membranes. But active transport, protein binding, and metabolism depend on highly chiral receptors, channels, transport molecules, and enzymes. In these latter processes, fates and reaction rates of enantiomers can be very different.

And analytical chemist Irving W. Wainer of St. Jude Children's Research Hospital, Memphis, Tenn., expressed a note of caution when he told the audience that chiral excipients may affect bioavailability of chiral drugs.

Excipients are seemingly inactive fillers used to formulate dosage forms like pills, tablets, and capsules. The ones most commonly used are lactose and microcrystalline cellulose, and there is great current interest in cyclodextrins. Also, sucrose is often used to make syrups palatable. These may interact differently with different enantiomers in racemates to produce different rates of dissolution and absorption.

The chiral excipient issue will affect generic as well as pioneering drug companies, Wainer says. This is because generic drug makers must formulate for bioequivalence when submitting abbreviated new drug applications (NDAs) to FDA.

As new FDA regulations on chiral drugs approach, analytical chemists at drug firms will have to gauge the impact on their work load. Analytical chemist Ronald J. Bopp of Eli Lilly & Co., Indianapolis, assesses the forms the impact might take.

One question is the strategy the company takes in developing compounds from research. In one approach, the company might do exploratory studies on racemates before deciding whether to study enantiomers. The second approach might be to study enantiomers from the start. The second route would be expected to have greater impact on the analytical laboratory, because chemists would have to devise a chiral assay for every promising compound.

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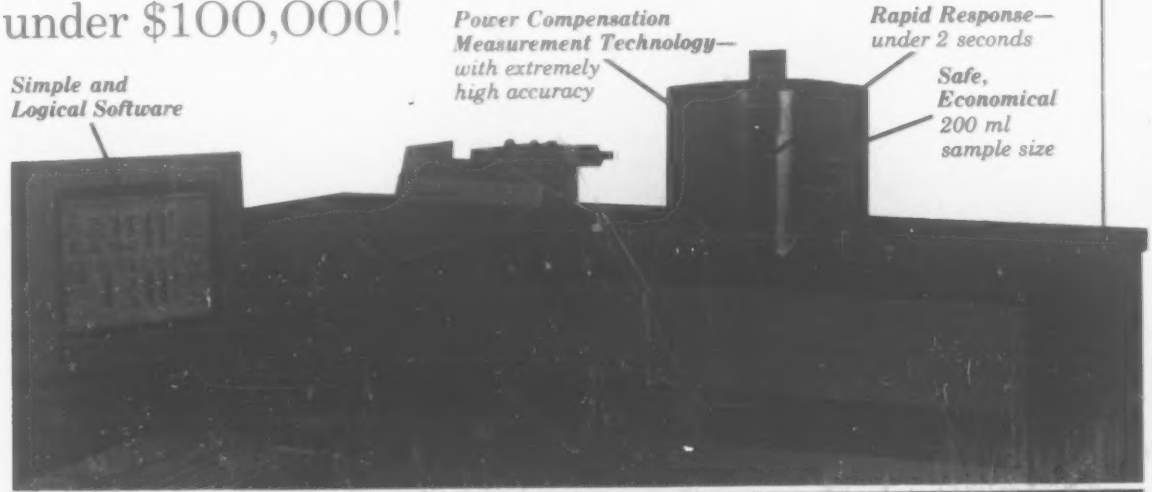
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By thinking ahead, chemists could save labor by recognizing the information content of every assay. In chiral high-performance liquid chromatography (HPLC), for example, the chiral stationary phase slowly racemizes with use. But Bopp demonstrated to the audience that what is important is relative peak heights, so column racemization need not cause trouble.

There is also the optical purity of derivatizing reagents. Chemists might be distracted by considering whether an analyte is 100% optically pure but the reagent slightly impure, or whether the reagent is pure but the compound is a mixture of enantiomers. Again, proper interpretation of chromatograms and attention to relative peak heights solves the problem.

Chiral assays need not be devised for every determination. Achiral assays are sufficient to determine purities of starting materials and intermediates. Also, for studies of compounds with two dissymmetric centers, metabolic inversion at one carbon produces a diastereoisomer, not the opposite enantiomer, and an achiral assay again suffices.

At any rate, chemists should use separate achiral assays for material purity and chiral ones to determine proportions of enantiomers. This is because one chiral assay might not solve both problems. And assays should be devised so that the enantiomer present in lesser amount elutes first so that it not be swamped in the tailing of the greater.

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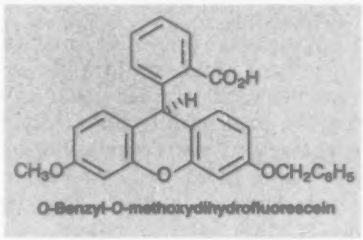
Chiral dye measures optical purity of chiral compounds



O-Benzyl-O-methoxydihydrofluorescein

Principal methods of chiral assays are HPLC, gas chromatography (GC), and thin-layer chromatography (TLC). Interest is also growing in supercritical fluid (SCF) chromatography and capillary electrophoresis. Pharmacology professor Anthony F. Fell of the University of Bradford, England, has surveyed 800 literature references to chiral assays over the past two to three years. Of these, more than 70% are to HPLC, 15% to GC, and 5% to TLC.

The three basic chiral HPLC techniques are derivatization of analyte enantiomers with optically active reagents, use of a chiral column packing, and use of a chiral eluting solvent. Derivatizing any two analyte enantiomers with optically active reagents produces a mixture of two diastereoisomers, which can be separated on conventional, achiral columns.

The derivatization reaction is often laborious, but analytical chemistry professor Ira S. Krull of Northeastern University, Boston, describes a simple method based on chiral reagents immobilized on resins. Working with graduate students Chun-Xin Gao and Asa Trogen and supported by the National Science Foundation, Pfizer, and Supelco, he attaches chiral chains to crosslinked polystyrene consisting of a pyridinium, L-proline, and 9-hydroxymethylfluorene.

Passage of solutions of racemic alcohols, amines, or mercaptans through the resin resulted in transfer of a chiral proline-fluorene group to the hydroxyl, amino, or sulfhydryl groups. Krull says this method avoids separation steps and that he can regenerate the derivatizing resin.

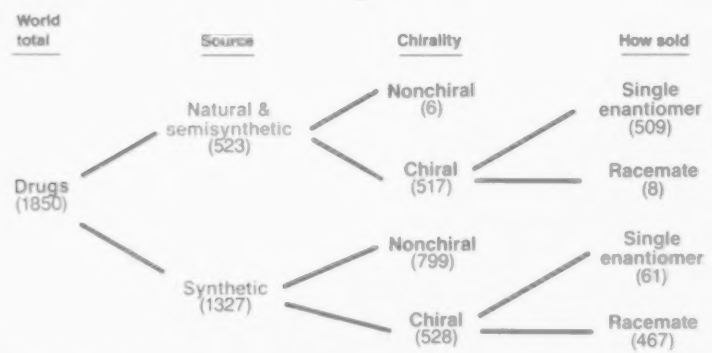
As the University of Bradford's Fell points out, about 50 chiral column packings are commercially available for HPLC. Most of these are of the Pirkle type, named for analytical chemistry professor William H. Pirkle of the University of Illinois, Urbana-Champaign, who made many of them and put forth the theory of their efficacy.

Pirkle column packings bear chiral units consisting of acidic, basic, or π-acceptor groups or acidic, π-acceptor, and steric interaction (bulky) groups. Such arrangements provide the three-point-landing array that gives the best recognition of opposite enantiomers.

However, interest is growing in proteins as sources of chiral column packings. Of these, Fell says that α_1-acid glycoprotein (AGP) has the greatest range of temperatures, solvents, and compound types. The Bradford pharmacologist ascribes the success of AGP columns to invention of a new generation of them by ChromTech of Norsborg, Sweden, and tradenamed Chiral-AGP. Jörgen Hermansson of ChromTech separately surveyed the utility of the company's columns.

Despite the apparent abundance

Most synthetic chiral drugs sold as racemates



Source: E. J. Ariëns, University of Nijmegen

of useful materials, devising chiral HPLC assays that meet the needs of the drug industry can be long and arduous. Fell suggests that one shortcut might be use of computer-guided factorial experiments in which two variables are changed in each experiment and the response measured.

For example, he cites finding the best combination of pH and percent of acetonitrile added as a modifier. He plots a three-dimensional graph he calls a response surface with pH along one horizontal axis, percent of modifier along the other, and response—degree of separation—along the vertical axis.

Visual inspection of the graph shows a peak response, but the exact location of the maximum is uncertain. Fell uses a simplex analysis of the response surface to find the maximum. In this technique, he uses a series of triangulations beginning at the edge of the surface to ascend, crablike as he puts it, to the maximum. Each triangulation leads to a point representing the experimental conditions to be tried next.

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The method has the advantage that the chemist need not know anything in advance about the response surface to explore it. But Fell admits the technique requires a lot of experiments, and the simplex analysis might get stuck at the top of a local maximum without finding the global maximum.

In such work, Fell advocates use of second-derivative functions of chromatogram peaks. These functions show with great sensitivity whether peaks are single or overlapped, and they indicate incipient separations.

One difficulty in devising chiral HPLC methods is that the samples are often blood serum or urine, and these contain other substances that must be separated to make the determination of enantiomer contents clearer. Wainer of St. Jude says the solution is often a coupled column approach, in which the sample passes first through an achiral compound to separate the chiral analyte of interest from others and then through a chiral column to assay the enantiomers. A switching valve diverts samples alternately to one detector to measure total concentration of racemic compound and a second detector to measure amounts of enantiomers.

But such methods can take hours. Faced with an emergency situation in which he had to monitor serum concentrations of (6*S*)-leucovorin in one patient, Wainer, measuring frequently, devised a method in which the sample passes first through a bovine serum albumin chiral com-

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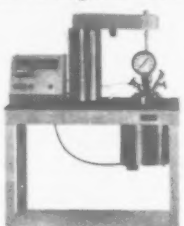

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pound and next through an achiral octadecyl column. The achiral column serves to compress the peaks. The resulting assay took only 70 minutes to do.

In addition to chiral HPLC, chiral gas chromatography (GC) has taken on new importance, thanks to analytical chemistry professor Daniel W. Armstrong of the University of Missouri, Rolla. His breakthrough was preparation of cyclodextrin derivatives that are both viscous liquids at room temperature and polar (they dissolve in water). Their liquid state eases the task of coating columns and gives a more dynamic interaction with chiral analytes.

The three cyclodextrins are cyclic oligomers of α-1,4 glucose units. α-Cyclodextrin is a hexamer, the β is a heptamer, and the γ is an octamer. The three hydroxyl groups of each glucose unit that are free for derivatization are called 2-OH, 3-OH, and 6-OH. Armstrong's group first reacts cyclodextrins with propylene oxide in aqueous sodium hydroxide, which may have attached 2-hydroxypropyl groups at 2-OHs. Subsequent reaction with methyl iodide produces permethyl-*O*-hydroxypropylcyclodextrins.

Columns coated with these derivatized cyclodextrins separated a wide variety of alcohols, amines, aminoalcohols, aminoethers, epoxides, larger cyclic ethers, lactones, and terpenes from one another and also separated enantiomers of each. The Missouri chemists convert amines and alcohols to trifluoroacetyl derivatives before injection onto columns. Armstrong notes that most of these compounds lack aromatic

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groups that seem necessary for chiral separations with HPLC.

Armstrong's coworkers in this project were polymer chemist research fellows Weiyong Li, Jo Dee Duncan, San-Chun Chang, and Randy A. Menges, along with research professor Apryll M. Stalcup at Rolla and polymer chemist Joseph Pitha at the National Institutes of Health. The Department of Energy supported their research.

Besides chiral HPLC and chiral GC, chiral supercritical fluid chromatography (SFC) has received attention from several research groups. Supercritical fluids are very dense gases maintained at high pressures above their critical temperatures. The critical temperature is the temperature above which a gas can no longer be liquefied by compression at any pressure. Typical supercritical fluids used in SFC are carbon dioxide, nitrous oxide, and sulfur hexafluoride.

Densities of supercritical fluids are 0.5 to 0.9 g per mL. These densities approach those of liquids commonly used as HPLC solvents. Thus solvent powers of supercritical fluids also approach those of polar liquid solvents. Such high solvent powers eliminate the need to vaporize analytes as is necessary in GC. Yet because they are gases, their flow rates are as high as that of helium in GC, leading to faster analyses than with HPLC. Indeed, chromatographers using SFC can program pressure rises into analyses, which means programing density profiles.

Research professor Karin E. Markides of Brigham Young University, Provo, Utah, described separation of enantiomers of *trans*-stilbene oxide using an open tubular column coated with a chiral compound and employing flame-ionization detection. Analyses were 10 times as fast as with HPLC. And flame-ionization detection was sensitive to minute amounts of sample. Markides points out that the trend in the drug industry is toward ever more potent compounds, which means that analytical chemists will be called on to detect ever smaller amounts.

In his contribution to chiral thin-layer chromatography, Arnold Brossi turned to classical dye chemistry. Brossi, who heads the natural products section in the National Institute of Diabetes, Digestive & Kidney Diseases, Bethesda, Md., uses chiral derivatives of fluorescein.

Postdoctoral fellow Dragana Tadic synthesizes these by reduction of fluorescein to dihydrofluorescein with sodium borohydride and making a mixed benzyl methyl ether of the resulting dihydroxy compound. The different substituents render the methine carbon asymmetric, and Tadic resolves the enantiomeric dyes. These can be used to make ester and amide derivatives of racemic alcohols and amines.

The NIH workers developed chromatograms of separated esters and amides by treating first with ammonium hydroxide and then with iodine. Ammonia cleaves the ether groups, rendering the resulting phenolic compound susceptible to iodination to spots of deep red erythrosine. Brossi's future work includes making fluorescein derivatives that are more easily cleaved during development of chromatograms.

Brossi predicts that these chiral dyes will find use in characterization of chiral natural products as well as assays of synthetic drugs because of the fact that several alkaloids occur as mixtures of enantiomers. □

Chirality issues spark a growth industry

Product category & application	U.S. sales ($ million) 1989	1995	2000	Average annual growth rate 1989–95	1989–2000
Analytical instruments & reagents	**$11.2**	**$14.4**	**$14.8**	**4.3%**	**2.6%**
Drugs	9.0	10.0	9.0	1.8	0
Nondrug applications	2.2	4.4	5.8	12.1	9.2
Separation products	**15.1**	**25.2**	**30.5**	**9.0**	**12.5**
Drugs	12.1	17.7	18.3	6.5	3.8
Nondrug applications	3.0	7.5	12.2	16.5	13.5
Reaction materials & catalysts	**438.5**	**1,280.7**	**2,749.1**	**19.5**	**18.2**
Drugs	350.8	902.1	1,649.5	17.0	15.0
Nondrug applications	87.7	378.6	1,099.6	27.5	26.0
TOTAL	**$464.8**	**$1,320.3**	**$2,794.4**	**19.0%**	**17.6%**

Source: Business Communications Co.